

Xanthogranulomatous cholecystitis: clinico-pathological study of 13 cases

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SUMMARY In a retrospective three year study 13 cases of xanthogranulomatous cholecystitis (XGC) (seven female, six male) were found in 724 gallbladders (1.8%), an estimated incidence of 1.7 cases per 100 000 population per annum. Symptoms often began with an episode of acute cholecystitis and persisted for up to five years. There was extension of xanthogranulomatous tissue into adjacent organs in nine cases. Three patients had fistulae from the gall bladder, one to skin, and two to the duodenum; this is the first report of this complication in XGC. In two patients XGC sufficiently resembled carcinoma for the surgeon to request intraoperative frozen section diagnosis. There was a high rate of postoperative infective complication, with one subphrenic abscess and three wound infections (one fatal), two in patients with fistulae.

Xanthogranulomatous cholecystitis (XGC) is an uncommon inflammatory disease of the gall bladder characterised by a focal or diffuse destructive inflammatory process, with varying proportions of fibrous tissue, acute and chronic inflammatory cells, and lipid laden macrophages. Macroscopically, areas of XGC appear as yellow masses within the wall of the gall bladder.

Xanthogranulomatous cholecystitis was first described in 1970 by Christensen and Ishak¹ as "fibroxanthogranulomatous inflammation." Since then over 60 cases have been described under a variety of synonyms, including "ceroid or ceroid-like histiocytic granuloma of gallbladder,"^{2,3} and "biliary granulomatous cholecystitis."⁴ The pathogenesis of XGC is uncertain, but reported opinion favours an inflammatory response to extravasated bile, possibly from ruptured Rokitansky-Aschoff sinuses.³ The true incidence of this apparently rare condition is difficult to establish; although Takahashi *et al*³ reported the incidence in Japan to be 1.2% of all surgically excised gall bladders, there has been no report of its incidence in a Western country.

In the studies where clinical information was available XGC was described as an uncomplicated mass in the wall of the gall bladder. Christensen and Ishak,¹ however, reported that in two of their 40 cases "the

question of a mesenchymal sarcoma was raised by the contributing pathologist."

In this paper we present the detailed clinical and pathological features and complications of the 13 cases of XGC presenting in a teaching hospital of 730 beds from 1983-85.

Material and methods

The files of the department of histopathology at the Royal Hallamshire Hospital, Sheffield, for the three years 1983-85, were examined retrospectively for cases of inflammatory disease of the gall bladder. A total of 724 surgically excised gall bladders were submitted for pathological examination during this period; among these, 13 cases of xanthogranulomatous cholecystitis were identified. The clinical records of these patients were reviewed for symptoms, signs, laboratory data, operative findings, and details of postoperative progress. Organ imaging data were obtained from the reports in the medical records. The macroscopic appearance of the gall bladder was compiled from the surgeons' notes and the detailed description in the pathologist's report.

After cholecystectomy the gall bladders were opened longitudinally and fixed in 10% neutral phosphate buffered formol saline. Sections were processed to paraffin wax, cut at 4 μ m, and stained with haematoxylin and eosin, periodic acid Schiff, Gram, Ziehl-Neelsen, Perl's Prussian blue and methenamine silver methods.

Tissue for intraoperative diagnosis was rapidly frozen, and cryostat sections cut at 8 μ m and stained with haematoxylin and eosin, and oil red O for fat.

Results

INCIDENCE

Thirteen cases of XGC were identified among 724 cholecystectomies performed over the three year period, an incidence of 1.8% of XGC in these gall bladders and an estimated incidence in the Sheffield area of 1.7 cases per 100 000 population per annum. There were 693 cases of chronic cholecystitis, six mucocoeles, three empyemas, and two carcinomas of the gall bladder.

The age of the patients with XGC ranged from 20 to 81 years with a mean of 63.2 years. This was significantly older than the mean age of 57.4 years of the patients with chronic cholecystitis ($p < 0.001$). Seven patients with XGC were female and six male; there was no significant age difference between the sexes.

SYMPTOMS AND PHYSICAL FINDINGS

Table 1 gives detailed clinical information in all 13 patients. The duration of symptoms ranged from six weeks to five years (mean 13.4 months). Eleven of the patients (85%) experienced at least one episode of acute cholecystitis, and for six, this was the first presentation of the disease. Four patients had no symptoms other than during the episode or episodes of acute cholecystitis. The time between the first episode of acute cholecystitis and surgery ranged from 1.5 to seven months (mean 3.8 months). The remaining three patients had a range of symptoms suggestive of cholelithiasis; right hypochondrial pain, nausea, vomiting, and intolerance of fatty foods. One patient developed acute pancreatitis. A fistula between the gall bladder and the skin in the right hypochondrium developed in one patient following an initial episode of acute cholecystitis and three months' intermittent abdominal pain.

Table 1 *Clinical findings*

<i>Clinical features</i>	<i>No of patients</i>
Acute cholecystitis	11
Symptom free between episodes of acute cholecystitis	4
Right hypochondrial pain	9
Nausea and vomiting	8
Fat intolerance	6
No abnormal physical findings	6
Right hypochondrial tenderness	6
Right hypochondrial mass	5
Fistula	1

ORGAN IMAGING

Ultrasound examination (table 2) was performed in all 13 cases.

LABORATORY FINDINGS

There were no consistent biochemical or haematological findings, other than neutrophil leucocytosis in acutely ill patients. The erythrocyte sedimentation rate was not determined in any patient.

OPERATIVE AND MACROSCOPIC FINDINGS (fig 1)

The gall bladders were surrounded by fibrous adhesions which were often extensive and attached to adjacent structures. The gall bladder wall was invariably thickened, and calculi of cholesterol or mixed type were present in all cases. Xanthogranulomatous foci appeared as nodules of yellow tissue 2–15 mm in diameter; although these were usually multiple, a single mass was present in one case. There was often some distortion of the adjacent gall bladder wall. In two of our cases the appearances of the xanthogranulomatous foci sufficiently resembled carcinoma for the surgeon to request intraoperative frozen section diagnosis.

In nine patients there was extension of yellow xanthogranulomatous tissue into adjacent structures, particularly liver, duodenum, transverse colon and omentum; two cases were associated with abscess formation in the adjacent liver. There were two cases of fistula extending from the gall bladder into duodenum and one case of a fistula between the gall bladder and the skin. In a further case a calculus had eroded the wall of the gall bladder, causing compression of the common bile duct and obstructive jaundice.

MICROSCOPIC FINDINGS

Histologically there was a focal or diffuse destructive inflammatory process with varying proportions of lipid laden macrophages, inflammatory cells, and fibroblasts.

Small foci of xanthogranulomatous tissue were centred on Rokitansky-Aschoff sinuses and confined to the gall bladder wall (fig 2). Larger destructive "tumour-like" masses encompassed the full thickness of the gall bladder wall, with variable extension into adjacent fat, and connective tissue, and mucosa.

Table 2 *Organ imaging findings*

<i>Ultrasound examination findings</i>	<i>No of patients</i>
Gallstones: gall bladder	13
bile ducts	1
Gall bladder wall thickened	8
Mass suggestive of carcinoma	3
Enteric biliary fistula (gas in biliary tree)	1

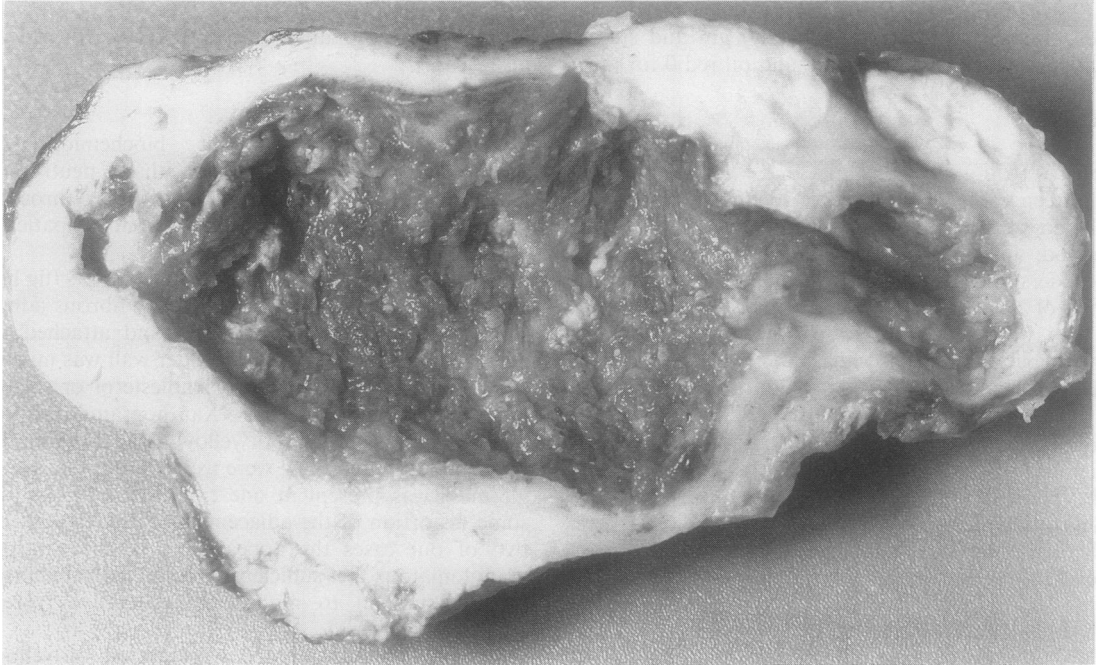


Fig 1 *Xanthogranulomatous cholecystitis. Tumour like deposits of xanthogranulomatous tissue are present within gall bladder wall.*



Fig 2 *Small focus of xanthogranulomatous tissue centred on Rokitansky-Aschoff sinus and confined to gall bladder wall.*

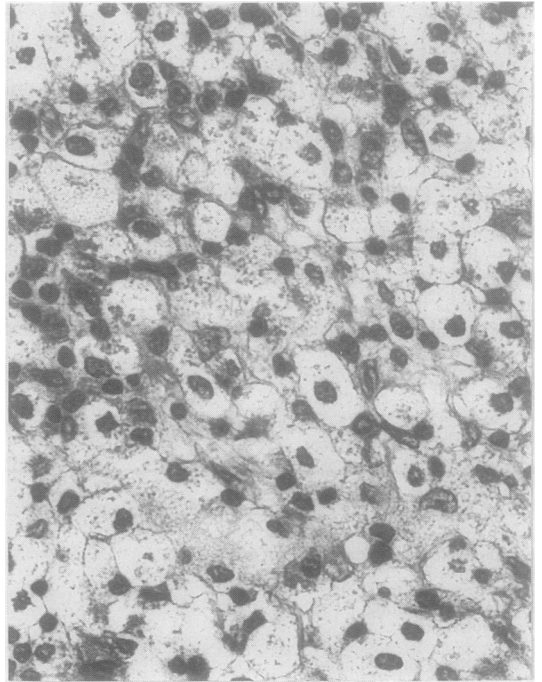


Fig 3 *Rounded macrophages present in small focus of xanthogranulomatous inflammation.*

Mucosal ulceration was present in six cases. Histological evidence of extension of XGC into the liver was seen in two cases.

Within xanthogranulomatous areas the lipid laden macrophages were of two morphological types; rounded "foamy" macrophages (fig 3) and spindle shaped cells (fig 4) with more granular cytoplasm and rather elongated nuclei. Both cell types were present in all lesions, although in the larger, tumour like foci, the cells were predominantly of the spindle shaped variety, with a tendency to form a storiform growth pattern (fig 5). In cases with small foci or with diffuse involvement of the gall bladder the xanthoma cells were predominantly rounded.

Cholesterol clefts, lipid droplets, haemosiderin deposits, giant cells of foreign body and Touton type and extravasated bile were present in most cases (fig 6). Epithelial remnants could be identified within many of the larger foci, and where this was not so, smaller xanthomatous areas could be identified round Rokitsansky-Aschoff sinuses adjacent to the main inflammatory mass. Many lymphocytes and fewer plasma cells, macrophages and eosinophils were variably present. In one case only was there superimposed acute cholecystitis.

In all cases of XGC the remainder of the gall bladder showed a variable, though usually severe, degree of chronic cholecystitis, often with lymphoid follicles. Table 3 summarises the principal findings.

CLINICAL OUTCOME

Eight of the 13 patients had an uneventful post-operative recovery. Three patients developed wound infections; two of these with associated sinuses, and one patient had a subphrenic abscess. One patient required partial gastrectomy to control haemorrhages from acute gastric erosions, followed by an episode of acute cholangitis. Although most patients eventually made a good recovery, one of the patients with a wound sinus became infected with an enterotoxin F producing *Staphylococcus aureus* and he died from the toxic shock syndrome 29 days after the operation.

Discussion

Xanthogranulomatous cholecystitis is generally believed to be a rare condition. Although in one series of 13 cases its incidence has been estimated to be 1.2% of all surgically excised gall bladders,³ it is impossible to determine its incidence in the population

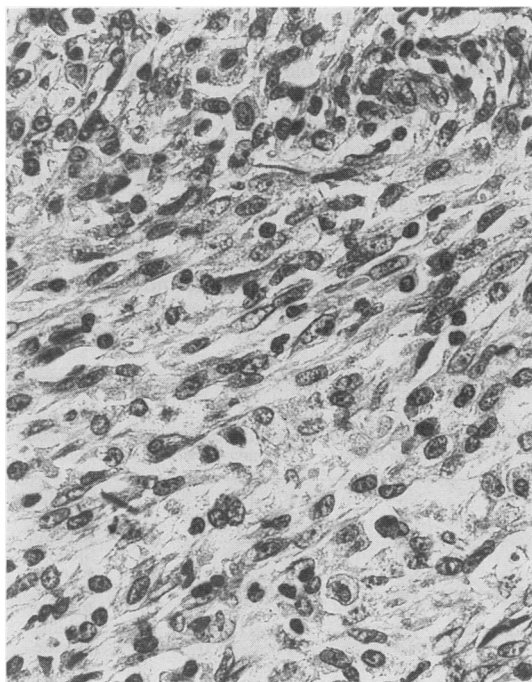


Fig 4 Spindle shaped cells from large, tumour like deposit of xanthogranulomatous tissue.

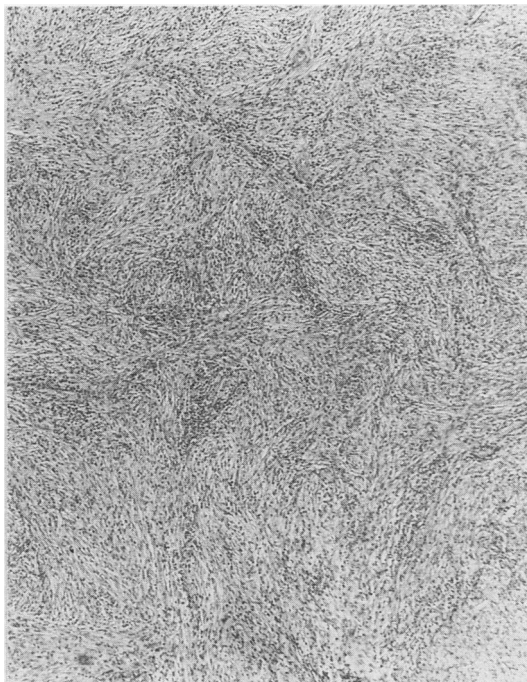


Fig 5 Storiform arrangement of spindle shaped cells seen in some large foci of xanthogranulomatous inflammation.

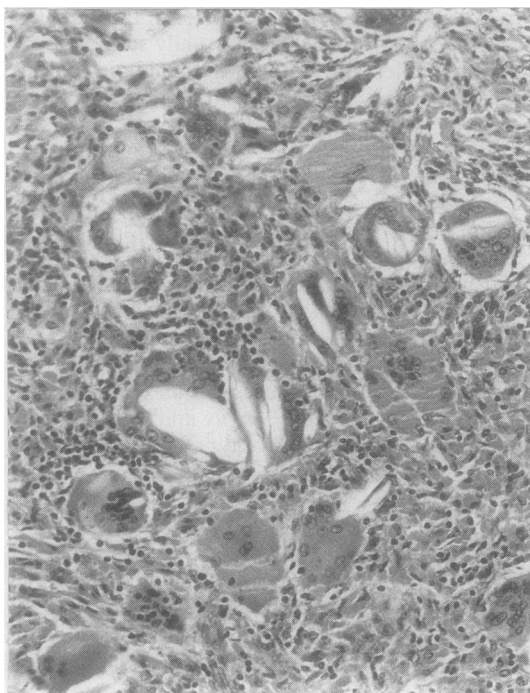


Fig 6 Giant cells and cholesterol clefts, often a feature of xanthogranulomatous cholecystitis.

from previous studies. The largest reported series of 40 cases⁵ was of material submitted from a wide area for review and no estimate of incidence was possible. In the present study we estimated the incidence of XGC in that area of Sheffield served by the Royal Hallamshire Hospital to be about 1.7 cases per 100 000 population per annum, with an incidence of 1.8% in surgically excised gall bladders. Although uncommon, the incidence of XGC in our study is greater than that of carcinoma of the gall bladder. Increasing

recognition and reporting of XGC should indicate the true incidence of this condition.

Although in our study patients with XGC were older than those with chronic cholecystitis (63.2 years v 57.4 years, $p < 0.001$), the age range is so great that this is unlikely to be useful clinically in the differential diagnosis. Overall, in the published cases, including this series, there is a slight female preponderance of 1.7 to 1, which probably reflects the increased incidence of cholecystitis in women.

Clinically, XGC may be difficult to distinguish from other inflammatory gall bladder diseases or cholelithiasis. Interestingly, however, 11 of our 13 cases had a convincing history of at least one previous episode of acute cholecystitis, and six of these patients had acute disease at presentation. This preponderance of acute initial episodes is unusual in chronic cholecystitis or cholelithiasis. Patients with XGC were not anaemic, as are many patients with the analogous renal condition, xanthogranulomatous pyelonephritis.⁶ Although the erythrocyte sedimentation rate was not determined in our cases, it is likely to have been raised, but not to the same degree as in patients with xanthogranulomatous pyelonephritis. Haematological changes are more likely in xanthogranulomatous pyelonephritis, with its generally larger volume of xanthogranulomatous tissue.

Physical examination and organ imaging are important in the preoperative assessment of patients with inflammatory gall bladder disease. Although six of the patients had no abnormal physical findings, five had a palpable tender mass in the right hypochondrium. Ultrasound examination was useful for showing universal cholelithiasis and thickening of the gall bladder wall in eight patients.

Three of the five patients with a hypochondrial mass had findings on ultrasound examination suggestive of carcinoma of gall bladder, and at operation in two of these patients the appearance of the gall

Table 3 Summary of findings

Case No	Duration of symptoms	Episode of acute cholecystitis	Calculi	Fistula	Extension into adjacent structures	Diffuse or focal disease (diameter mm)	Type of xanthoma cell
1	18 months	6 months	Yes	No	No	Focal (7)	Spindle
2	6 weeks	6 weeks	Yes	No	Entericbiliary	Focal (8)	Spindle
3	2 months	2 months	Yes	No	No	Diffuse	Round
4	7 months	7 months	Yes	No	No	Focal (6)	Spindle
5	9 months	None	Yes	No	No	Focal (2)	Round
6	3 years	3 months	Yes	Entericbiliary	Yes	Diffuse	Round
7	4 months	4 months	Yes	No	Yes	Focal (1.5)	Round
8	18 months	6 months	Yes	Gall bladder skin	Yes	Focal (15)	Spindle
9	3 years	3 months	Yes	No	No	Focal (5.5)	Spindle
10	2 months	2 months	Yes	No	Yes	Focal (8)	Spindle
11	10 months	5 months	Yes	No	No	Focal (8.5)	Spindle
12	3½ months	None	Yes	No	No	Focal (3)	Round
13	3 months	3 months	Yes	No	Yes	Focal (9)	Spindle

bladder sufficiently resembled carcinoma for the surgeon to request rapid frozen section diagnosis. The ability of XGC to resemble carcinoma clinically and macroscopically is further complicated by its ability to mimic tumours histologically. Confusion with a neoplasm is perhaps most likely where spindle shaped xanthoma cells predominate with a storiform growth pattern. XGC lacks true malignant features, such as pleomorphism, cellular atypia, and increased or bizarre mitotic figures. An awareness of the condition and good liaison with the clinician is required so that interpretation of histological findings may be made in the light of clinical, organ imaging, and macroscopic findings; this is of particular importance in rapid frozen section diagnosis, where a small sample may exacerbate the problem.

An important complication of XGC, which has not been reported previously, is the development of fistulae, present in three of our cases and otherwise rare in cholecystitis. Thus XGC seems to share the potential for fistula formation with xanthogranulomatous pyelonephritis, where fistula formation is well recognised.⁶⁻⁹

The pathogenesis of XGC is unclear, although the role of cholesterol and bile is thought to be important.^{2-5,10} Bile degradation within histiocytes as a cause of the xanthoma cells has been proposed.² Takahashi *et al*³ and Goodman and Ishak⁵ have suggested that the important event is the extravasation of bile into the gall bladder wall, either from ruptured Rokitsky-Aschoff sinuses or focal mucosal ulceration. Fligel and Lewin¹⁰ believe that in addition to the presence of bile, a more important feature may be a long standing or recurrent inflammatory process. They also draw the analogy to xanthogranulomatous pyelonephritis, where obstruction with stasis is important, and suggested the possible role of gallstones in causing obstruction in XGC. In the largest published series of cases of XGC gallstones were present in only three quarters of the cases; in our series they were present in all cases. In most cases foci of XGC seem to be centred on Rokitsky-Aschoff sinuses.

We believe that the pathogenesis of XGC is similar to that proposed by Parsons *et al* for xanthogranulomatous pyelonephritis.⁶ The essential ingredients are inflammation associated with infection, obstruction of the biliary outflow from the gall bladder due to calculi, and a source of lipid—in this case biliary cholesterol. A gall bladder with partial or total obstruction of bile outflow by calculi becomes acutely inflamed, most probably as a result of infection. This results in rupture of Rokitsky-Aschoff sinuses or mucosal ulceration with subsequent extravasation of bile into the gall bladder wall. Histiocytes accumulate in an attempt to phagocytose the biliary cholesterol and xanthoma cells form. As the lesion increases in size some of the fat within the xanthoma cells may be derived from adipose tissue on the serosal surface of the gall bladder or from adherent omentum. With

time, organisation of the inflammatory mass occurs and eventually the xanthoma cells elongate into a spindle shaped configuration and fibrosis increases. It is at this stage that confusion with a neoplasm is most likely. Failure of drainage of the inflammatory infiltrate in the acute phase may lead to extension of the xanthogranulomatous inflammation beyond the gall bladder with the formation of abscesses, sinuses, or fistulae draining to bowel, skin, or elsewhere.

We support the view of Goodman and Ishak⁵ that the best name for this condition is xanthogranulomatous cholecystitis as this emphasises its inflammatory nature and its conceptual similarity to the renal condition, xanthogranulomatous pyelonephritis. We believe XGC deserves recognition as a distinct clinicopathological entity, not only because of its possible confusion with malignancy but also because of its associated complications.

Surgery is likely to be complicated by the presence of dense fibrous adhesions, abscesses, and adherence of the gall bladder to adjacent structures. Post-operative wound infection or sinuses seem disproportionately common. As the condition has the potential for fistula formation, percutaneous needle biopsy is probably contraindicated, and it may be necessary to confirm the benign nature of the lesion by intraoperative frozen section diagnosis.

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